ABSTRACT

THESIS: Determining the Effects of the Major G-quadruplex helicase, G4R1, on Motor and Cognitive Functions in Mice

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G-quadruplexes are guanine-rich nucleic acid secondary structures enriched in regulatory regions. Formation of G-quadruplexes typically imparts negative regulation to major cellular processes. G-quadruplexes regulate neuronal trafficking and local translation of hundreds of transcripts at the dendritic synapse and disruption of G-quadruplex processes is frequently reported in neuromuscular diseases. G-quadruplexes are modulated by specialized helicases that bind and unwind these structures. One such helicase is G-quadruplex Resolvase 1 (G4R1; aliases DHX36 and RHAU). G4R1 is the major human G-quadruplex helicase with dual specificity for DNA and RNA G-quadruplexes. G4R1 is highly expressed in neurons and involved in many developmental processes. It was unknown if G4R1 is implicated in motor and cognitive functions in mice. I hypothesized that G4R1 is important for normal neuronal functions, and consequently normal motor and cognitive functions in mice. I expected that a whole body *G4R1*-knockout would cause impaired motor and cognitive functions in adult mouse similar to the ones observed in neuromuscular diseases. Considering the importance of G4R1 during development, I further hypothesized that these phenotypes would be more severe the earlier *G4R1* is knocked-out. To test this, I established a new *G4R1*-inducible knockout mouse colony in the Smaldino lab. Next, I used a series of behavioral assays to determine the effect of *G4R1* loss

on motor and cognitive functions in young and adult mice. I found that G4R1 is essential to young mice survival. Thus far, my data suggests that G4R1 deletion does not affect adult mouse motor and cognitive functions. These data show for the first time that G4R1 is essential during early post-natal development, while further studies will be required to establish a role for G4R1 on mouse motor and cognitive behaviors, perhaps with larger sample sizes.